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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,586	12/12/2005	Gabriele Multhoff	KNAUTHE-09734	3810

7590 03/06/2007
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EXAMINER

YOUNG, HUGH PARKER

ART UNIT	PAPER NUMBER
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1654

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/526,586	Applicant(s) MULTHOFF, GABRIELE	
	Examiner Hugh P. Young	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16-20 and 24-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16-20 and 24-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This is the first Office action on the merits of application No. 10,526,586. There are nine claims pending, fifteen of the original twenty-four having been cancelled and four new claims simultaneously added.

Election/Restrictions

1. Applicant's election with traverse of Group IV, claims 16-20, 24 and 25-28, as well as the election with traverse of the species of disease or condition treated to be tumor cells, in the reply filed on Dec. 18, 2006 is acknowledged. The traversal is on the ground(s) that the grouping of the claims into Groups IV, V and VI is not supported because the cell types, disease and conditions to be treated are linked by having Hsp70 expressed on the cell surfaces. This is not found persuasive because the invention is directed to the use of Granzyme B as the active agent, and Applicant's disclosure does not indicate that there is any physical separation or differentiation of the target cells to be treated other than the increased presence of Hsp70 on those cells, and that the art teaches that Granzyme B is naturally present from several sources and able to contact cells irrespective of the presence or absence of Hsp70.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 24 and 28 were originally withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. During examination of the elected species, however, the Examiner found art relevant to the species (viruses) of claims 24 and 28 and

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subsequently rejoined them to this Action. Applicant timely traversed the restriction (election) requirement in the reply filed on December 18, 2006.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 16-20 and 24-28 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The two methods claimed, the method of contacting NK-cells with tumor cells (claims 16 and 18-20) and the subsequent action of Granzyme B (instant claims 17 and 25-28) occur naturally as part of the immune response, whether innate or induced. Wever et al. (1997; *J. Histochemistry & Cytochemistry*, 45:467-469) teach that Granzyme B is found in circulating blood lymphocytes of healthy individuals (Conclusion; last paragraph, left-hand column, page 469), thus showing that lymphocytes containing Granzyme B are always present and on guard to defend the body; furthermore the second two steps of the instant method, allowing Granzyme G to enter the cell and allowing apoptosis to occur, are both naturally-occurring events that usually happen once the lymphocytes have contacted a target cell.

Claims 17 and 25-28 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The method claimed, contacting tumor cells with Granzyme B, occurs naturally. Spaeny-Dekking et al, (1998; *J.*

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Immunology, 160:3610-3616) teach that Granzyme B is detectable in humans extracellularly, circulating in the blood and other extra-cellular fluids, presumably as a result of "leakage" concomitant to ongoing lymphocyte activity (Fig. 5 right-hand column, page 3613; Table I, page 3614). Thus, Granzyme B is naturally present and available to perform any functions inherent to it; furthermore the second two steps of the instant method, allowing Granzyme G to enter the cell and allowing apoptosis to occur, are both naturally-occurring events that usually happen once the lymphocytes have contacted a target cell. In addition, Spaeny-Dekking et al. show, also in Fig. 5 and Table I (cited supra) that patients with elevated immune-response activity (rheumatoid arthritis) were naturally exhibiting elevated titers of Granzyme B without any medical intervention, suggesting that, whatever the stimulus or disease, lymphocytes release Granzyme B into the circulating blood or lymph. The Discussion presented by Spaeny-Dekking et al, (second paragraph, right-hand column, page 3614) reiterates that extracellular Granzymes are present in healthy blood donors; furthermore they teach that their experimental protocol was not able to determine whether the Granzymes present were there as a result of induced degranulation by the lymphocytes or from constitutive secretion of same. Finally, Shi et al. (1997; *J. Experimental Medicine*, 185:855-866) teach that Granzyme B autonomously crosses the cell membrane, without perforin being necessary. This indicates that freely-circulating Granzyme B, whatever its origin, is naturally available and able to penetrate those cells it contacts, should they be receptive (including those expressing Hsp70 cells).

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 16-20 and 24-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Srivastava et al, in U.S. Patent No. 6,130,087, issued October 10, 2000 (filed October 7, 1996). Srivastava et al. teach methods for generating antigen-reactive T-cells, in vitro, by contacting T-cells with cancer cells or infected cells (Column 8, lines 21-32), with the advantages that the T-cells could be primed and sensitized to the target cells, much as would happen in vivo as a result of vaccination, except that the target cells in question, cancers and infected cells, were too dangerous to inject into a subject. It can be appreciated that any target cells expressing Hsp70 on their surface would thus be providing Hsp70 as a recognition-marker as well as allowing any Hsp70 present to provide whatever other stimulation to the T-cells as occurred, naturally, such as stimulation of Granzyme B production. Srivastava et al. further disclose (column 14, lines 20-43) an exemplary method, using a non-limiting protocol, for co-incubating cancer or infected cells with T-cells, optionally with heat shock proteins or peptides provided by or from the target cells in order to enhance the efficiency of the in vitro priming reaction. Indeed, in section 5.4, column 14, lines 1 et seq., Srivastava et al. provide a protocol for obtaining and purifying heat-shock protein complexes, including those of Hsp70, in order that they may be provided to the T-cell/target-cell culture as

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recited above. Srivastava et al. claim methods that anticipate the instant claims 16 –20 and 24-28 in their claims 1, 3-9, 11-16, in which they claim the methods indicated above.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 16-20 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trouet et al., US Patent Application Publication US 2004/0014652 A1, published January 22, 2004 (PCT/EP01/06106 filed May 29, 2001, and drawn to US 60/208,996, filed on June 1, 2000).

9. Trouet et al. teach Granzyme B as an agent for treatment of tumors and cancers (paragraphs [0013], [0139], [0140-0141], and [0277-0281]) and claim Granzyme B as an agent in compositions for treating cancer cells in claims 29, 35, and 51. Trouet et al.

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disclose the addition of a masking or protecting moiety to Granzyme B, among other agents of interest, in order to give it more protection from proteases and peptidases present in the circulatory system as well as allowing it to penetrate the nuclear membrane more readily once it is in the cell. It is known in the art that Granzyme B is present in patients, especially but not exclusively near cells that are cancerous, infected or inflamed. The invention of Trouet et al, the addition to a naturally occurring substance of something to delay or reduce its destruction by enzymes, is not necessary for the naturally occurring function of Granzyme B, namely entering those body cells that are expressing the receptor/chaperone Hsp70 on their surfaces, to occur, albeit at natural, un-enhanced levels. Eliminating the optional, unnecessary artificial step of coupling native Granzyme B to a protective or chaperone moiety is a prima facie obvious step of simplification by eliminating an unnecessary step. It is obvious that the step of practicing Trouet et al's invention and adding these moieties to the natural product Granzyme B is not necessary because the natural state of Granzyme B, in healthy or unhealthy patients, is to lack these moieties. The invention of Trouet et al. is a potential improvement, certainly a change of, the natural product Granzyme B, but not a necessary one. The use of the modified Granzyme B product of Trouet et al. is obvious because the intended use of an anti-tumor or anti-cancer agent is to be used in the treatment of patients. In regards dosages to be used, Trouet et al. do not teach specific in vitro concentrations to be administered or patient-titers to be administered or maintained, but do teach (paragraph [0189]) that therapeutically effective and safely tolerated amounts of the compositions should be used, and do broadly teach how to use

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findings from cell culture (paragraph [0184]) and animal studies ([0205]) to determine safe and effective doses and dosing schedules suitable to the organism, disease and agent being used.

10. Claims 16 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Multhoff, G., US Patent No. 6,261,839 B1, issued July 17, 2001 (filed March 22, 1999), and drawn to DE 198 13 759, filed on May 27, 1998.

11. Multhoff, G. teaches a method of treating NK cells, ex vivo, by co-incubating them with target (tumor) cells, and heat-treating them with elevated temperatures and in the presence of a stimulatory irritant compound in order to induce the NK (natural killer cells) to then exhibit an enhance immune response to target (cancer), as stated in the Abstract and Claims 1-4 of 6,261,839. It obvious to eliminate unnecessary steps in order to practice a method or process and still achieve the original intended goal or purpose. The elimination of the two stressors, heat and a toxic chemical provided in sublethal amounts, simplifies the overall process and has the possible added advantage of leaving the NK cells in better condition.

Conclusion

12. No claims are allowed. As indicated supra, the non-elected species of disease, viral infection, was rejoined for purposes of examination on the merits.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hugh P. Young whose telephone number is (571)-272-4988. The examiner can normally be reached on 8:00 AM - 5:00 PM.

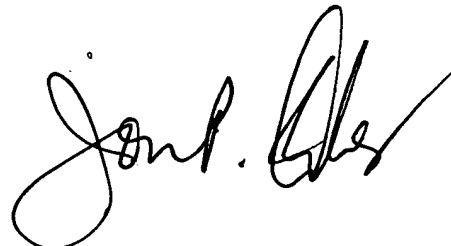
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hugh P. Young Ph.D.

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JON WEBER
SUPERVISORY PATENT EXAMINER